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Wilkinson, Michael H.F.

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Mathematical Modelling of Predatory Prokaryotes

Michael H. F. Wilkinson

Institute for Mathematics and Computing Science, University of Groningen, PO Box 800, 9700 AV Groningen, The Netherlands
m.h.f.wilkinson@rug.nl

Abstract Predator–prey models have a long history in mathematical modelling of ecosystem dynamics and evolution. In this chapter an introduction to the methodology of mathematical modelling is given, with emphasis on microbial predator–prey systems, followed by a description of variants of the basic two-species system. Then the two-species system is extended to incorporate effects such as predator satiation and prey escape strategies, after which multi-species effects, including alternative prey, protector species and decoy effects, are discussed. Simulations are used to discuss the effect of several model parameters.

1 Introduction

Mathematical models of predator–prey systems are amongst the oldest in biology (Lotka 1925; Volterra 1926). Though usually referred to as predator–prey systems, host–parasite and plant–herbivore systems are in many ways fundamentally the same: one species grows at the expense of another (e.g. Bulmer 1994; DeAngelis 1992). The mathematical treatment is therefore often similar, so predator–prey models are really a cornerstone of ecological modelling. Many, and certainly all the earliest, predator–prey models were concerned with macroscopic organisms. Though it has been shown that microbial ecosystems require a slightly different approach in some aspects, many of the same effects apply to all scales (e.g. Jost et al. 1973; Marchand and Gabignon 1981; Kooi and Kooijman 1994a).

This chapter has three main objectives: (1) to give a review of modelling predator–prey systems in general, (2) to review such work that has focussed on *Bdellovibrio bacteriovorus* and related species, and (3) to discuss a number of hypotheses proposed in other predator–prey systems in the context of predatory prokaryotes.

The chapter is organized as follows. First, modelling methodology is discussed, dealing with some basic concepts from dynamical systems theory. After this, various predator–prey models will be discussed, starting with the classical Lotka–Volterra model (Lotka 1925; Volterra 1926), followed by the introduction of variants to account for predator satiation and limitations on prey growth. Different models specific to the predatory prokaryotes are dealt with after this, including a comparison to bacteriophage models. Various strategies exist for bacterial predators, and the differences in modelling these mathematically are also dealt with. Furthermore, some models for evasion strategies for the prey are discussed.

In most cases I will assume the ecosystem is perfectly mixed (such as in chemostats), which means the spatial dimensions can be ignored. Certain ecosystems are not modelled well using this assumption, so techniques for dealing with spatial distributions and transport processes are dealt with briefly in Sect. 2.2.

Of course, no real ecosystem consists of just one predator and one prey. Therefore, multiple-species effects are dealt with after that. The most important of these are the alternative prey (Mallory et al. 1983), protector species (Pius and Leberg 1998) and decoy effects (Christensen et al. 1976; Wilkinson 2001). Though some of these have been suggested or even observed in a microbial setting, the protector species effect has not. A model for this effect in the context of predatory prokaryotes is presented here. The chapter ends with a discussion of the state of the art in modelling predatory prokaryotes and future directions for research.

2
Methodologies in Ecological Modelling

Mathematical modelling of ecosystems has two major aims, which are closely related: (1) understanding the dynamics of the system, given the behaviour of the organisms within the system, and (2) understanding the evolutionary processes by which different behaviours occur. Two approaches to modelling have been used traditionally: (1) dynamical systems, in particular through the use of differential equations, and (2) game theory, which focuses on best choices of behaviour given some model for the "payoff" of each possible strategy. These two approaches are no longer considered to be completely separate: replicator equations yield game-theory-based dynamical systems (e.g. Hofbauer and Sigmund 1998). Other taxonomies of modelling approaches split models into *tactical* and *strategic* models (Levins 1968). The former aim at accurate predictions for a specific system, but low general applicability, whereas the latter aim at wide applicability, but without accurate predictive capability. Strategic models are mainly interested in what kind of dynamics may occur in a given class of systems. We may also distinguish between individual-based modelling, in which the population is represented as a system of N interacting individuals, versus population-density-based modelling, in which the system is represented by M densities, each representing a particular species (generally $M \ll N$). It is assumed that each of the densities is a continuous variable, which is plausible if the populations are large enough. Density-based models are far easier to treat analytically, whereas individual-based models can handle inter-individual difference within a population more easily, potentially showing a richer diversity in behaviour. This is why individual-based modelling has become popular only after the availability of (lots of) cheap computing power. Fortunately, the population numbers in microbial predator–prey systems easily run into billions of individuals, so modelling on a population density basis is feasible, which is why the main focus is on this type of modelling.

Many textbooks on theoretical (evolutionary) ecology exist (e.g. Bulmer 1994; DeAngelis 1992; Hofbauer and Sigmund 1998; McGlade 1999), each of which provides a solid background in the topic of predator–prey modelling. A specific textbook on mathematical modelling in microbial ecology is by Koch et al. (1998).

2.1
Dynamical Systems

The cornerstone of population modelling is through dynamical systems. A dynamical system is represented mathematically by its state variables. In typical predator–prey systems, the two most obvious state variables are predator density and prey density. In general we will have an N-dimensional

state vector $\boldsymbol{x} = (x_1, x_2, ..., x_N)^{\mathrm{T}}$, in which each x_i represents, for example, a species or resource density. Apart from the state vector, a dynamical system is defined by its differential equation, which has the general form

$$\frac{\mathrm{d}\boldsymbol{x}}{\mathrm{d}t} = \boldsymbol{f}(\boldsymbol{x}, t)\,, \tag{1}$$

in which $\boldsymbol{x}$ is some (vector-valued) function, which takes the state vector $\boldsymbol{x}$ and time t as its inputs, and returns the rate of change of the state vector. In other words, the rate of change in time of each of the state variables is determined by the current state of the system, and the time. The latter may be used to introduce circadian or seasonal effects into biological systems, or any other time-dependent external influence. In many cases, and indeed most of the cases reviewed in the rest of the chapter, we are interested in *time-independent* ordinary differential equations (ODEs) which ignore the influence of time, i.e.

$$\frac{\mathrm{d}\boldsymbol{x}}{\mathrm{d}t} = \boldsymbol{f}(\boldsymbol{x})\,. \tag{2}$$

In this case, we can study the equilibrium condition

$$\frac{\mathrm{d}\vec{x}}{\mathrm{d}t} = \boldsymbol{f}(\boldsymbol{x}) = 0\,,$$

or

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = f_i(\boldsymbol{x}) = 0\,, \quad \text{for all} \quad i \in \{1, 2, ..., N\}\,, \tag{3}$$

in which f_i denotes the ith element of $\boldsymbol{f}$. Each of these N equations yields a *zero-isocline* for state variable x_i, which is a manifold in N-dimensional space along which the rate of change of x_i is precisely zero. In 2-D these zero-isoclines are just curves, in 3-D they are curved surfaces. The equilibrium points are found where all N isoclines intersect. An example is shown in Fig. 1c,d, in which the zero-isoclines for prey and predator are drawn for a predator–prey system. Thus, solving for equilibrium requires solving N (non-linear) equations. Given the non-linear nature of the equations, there may be any number of equilibria. Each of these equilibria can be (locally) stable, neutrally stable, or unstable. If the system is in a stable equilibrium it will return to the same state after any small disturbance. Neutral stability means that the system will not return to equilibrium, but neither will it move further away if disturbed. Instability means that a small disturbance will cause the system to move ever further from the equilibrium. In the case of time-independent ODEs, we can perform *local stability analysis* of the result very easily (e.g. DeAngelis 1992).

Rather than simply focussing on equilibria, we often want to use ODEs to determine the evolution of the state of the system in time. In the simplest cases, an exact, analytical solution can be computed, but often we have to

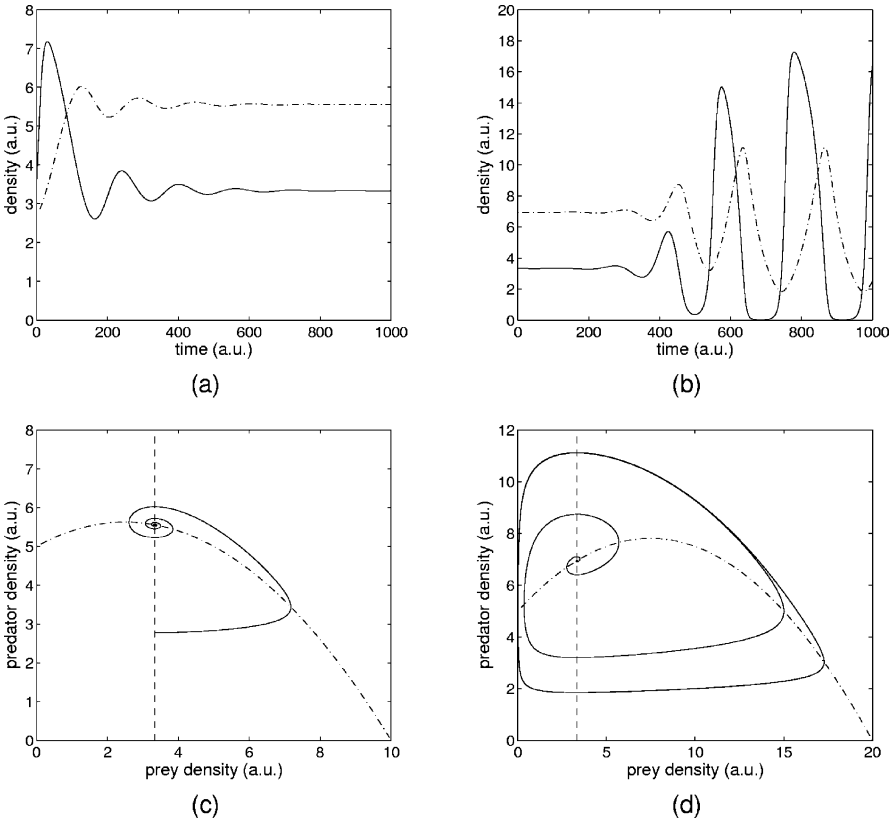

Fig. 1 Predator–prey dynamics using logistic growth for prey and Holling type II for the predator. **a** Predator (*dash-dot line*) and prey (*solid line*) densities vs. time, for carrying capacity $K = 10$; **b** same as **a** but with $K = 20$; **c** and **d** predator vs. prey density (*solid line*) for the same settings as **a** and **b**, respectively. The predator (*dashed line*) and prey (*dash-dot line*) zero-isoclines are shown as well. In the case of $K = 10$ the system stabilizes, even when released far from equilibrium, whereas for $K = 20$ the system spirals away from equilibrium for even the smallest perturbation. a.u.: arbitrary units

resort to numerical treatment. The most common type of problem concerning ODEs is the so-called initial value problem. In this case the state of the system is known at some time t_0, and we wish to compute the state of the system at a series of points in time t_1, t_2,...,t_m. This can be done using one of many ODE solvers, the best-known of which are probably the Euler method and the Runge–Kutta method (Press et al. 1986; Van Loan 1997). Various scientific packages such as MATLAB (The Mathworks, Inc.) contain a variety of methods to solve ODEs, both analytically and numerically (Palm 2005; Van Loan 1997).

A variant of ODEs are *delay differential equations* (DDEs), in which the rate of change does not only depend on the current state of the system $\boldsymbol{x}(t)$,

but also on the state at various points in the past $\boldsymbol{x}(t-\tau_1), \boldsymbol{x}(t-\tau_2), \ldots, \boldsymbol{x}(t-\tau_K)$. Their general form is

$$\frac{\mathrm{d}\boldsymbol{x}}{\mathrm{d}t} = \boldsymbol{f}\left(\boldsymbol{x}(t), \boldsymbol{x}(t-\tau_1), \boldsymbol{x}(t-\tau_2), \ldots, \boldsymbol{x}(t-\tau_K)\right) , \tag{4}$$

and the equilibrium condition becomes

$$f_i\left(\boldsymbol{x}(t), \boldsymbol{x}(t), \ldots, \boldsymbol{x}(t)\right) = 0 , \quad \text{for all} \quad i \in \{1, 2, \ldots, N\} , \tag{5}$$

because $\boldsymbol{x}(t) = \boldsymbol{x}(t-\tau_j)$ for all j at equilibrium. Though finding equilibria is often straightforward, and similar to the ODE case, stability analysis and numerical treatment are in general more difficult in the case of DDEs. However, packages such as MATLAB also support DDE solvers. DDEs have been used to model bacterium–phage systems (Campbell 1961; Levin et al. 1977; Bohannan and Lenski 1997) and *B. bacteriovorus–Escherichia coli* systems (Marchand and Gabignon 1981; Dulos and Marchand 1984; see also Sect. 3.3).

2.2 Spatial Models

In the population-density models presented previously the spatial extent of the ecosystem was ignored. This may be done for two reasons. First, the analysis of the system becomes much easier. Second, spatial extent is irrelevant if the ecosystem is well mixed, as in a chemostat (excluding surfaces supporting biofilm growth). Including spatial extent can have a profound effect on the dynamical behaviour of an ecosystem. For example, the chaotic oscillations predicted by a non-spatial model for a gypsy moth population were changed into regular wave trains by diffusion in a spatial model of the same population (Wilder et al. 1995). Generally, when introducing a spatial dimension to the system we must change the ODEs to partial differential equations (PDEs), due to the transport processes. The simplest and most commonly used transport process is diffusion, which for any substance X is modelled using the following PDE:

$$\frac{\partial X}{\partial t} = d\nabla^2 X = d\left(\frac{\partial^2 X}{\partial x^2} + \frac{\partial^2 X}{\partial y^2} + \frac{\partial^2 X}{\partial z^2}\right) ,$$

in which ∇^2 is the Laplacian (a second-order spatial derivative) and d is a diffusion constant. If only diffusion is used, the system becomes a reaction–diffusion system, in which the growth model determines the type of reaction. PDEs are generally more difficult to handle, both analytically and numerically. To allow computer simulation, the spatial extent is discretized in some way, after which the PDE can be turned into a (complex) ODE. An introduction to solving PDEs numerically is found in the book by Press et al. (1986).

Spatial extent can be added in various stages, each adding complexity to the model. In microbial ecology, much work is done in chemostats (Monod

1950; Levin et al. 1977; Chao et al. 1977; Gerritse et al. 1992; Kooi and Kooijmans 1994a,b), eliminating the need for spatial extent in the mathematical model. A slightly more complex approach is to use N cascaded chemostats, the effluent of number i being the inflowing material for $i + 1$, thus effectively discretizing the spatial extent into N compartments (Itoh and Freter 1989; Gibson and Wang 1994; Alander et al. 1999; Forde et al. 2004). This can readily be modelled using mN coupled ODEs, with m the number of coupled ODEs needed to model a single chemostat. For the intestinal microbial ecosystem, one spatial (axial) dimension can be added in models of plug-flow reactors (Ballyk and Smith 1999; Ballyk et al. 2001; Jones and Smith 2000), in which PDEs are used to model transport, and ODEs growth and wall attachment. A 2-D approach (one axial, one radial dimension) has also been used for the same ecosystem, in the MIMICS cellular automaton (Kamerman and Wilkinson 2002; Wilkinson 2002).

Full-blown PDE-based analysis in microbial ecosystems is essential in, e.g., microbial mats (de Wit et al. 1995) or sediments (Jahnke et al. 1982), which may show a distinct layered structure. They have also been used to explain the diversity of bacteriocins in microbial populations (Frank 1994). Frank's analysis is a two-stage approach: first several coupled ODEs are used to analyse the dynamics of a system consisting of a bacteriocin-producing species and a susceptible species in a chemostat-like environment. This system is bistable: either the susceptible species survives, or the producer survives, but coexistence is impossible. He then extends the model to include a spatial dimension in which several nutrient-rich patches separated by low-nutrient regions exist. In this system coexistence of susceptible and producer species is possible. A slightly different lattice-based spatial model used by Isawa et al. (1998) yields a similar result. Other spatial models include those of bacterial chemotaxis, reviewed by Ford and Cummings (1998), and pattern formation in growing colonies (Ben-Jacob et al. 1995; Tyson et al. 1999; Kawasaki et al. 1997) and various biofilm models (Dockery and Klapper 2001; Hermanowicz 1998).

As a final note it should be said that other forms of structure within a population, such as size structure, age structure, or resource–reserve structure, can equally be modelled through PDEs, as in the dynamic energy budget model of Kooijmans (1993) which has been applied to microbial predator–prey systems (Kooi and Kooijmans 1994a,b).

3
Two-Species Systems

In the following discussion X will denote the number, biomass or density of the prey species, and Y will denote the number, biomass or density of the predator species. The classical model of predator–prey systems is the Lotka–

Volterra system, which is set of ODEs of the form

$$\frac{\mathrm{d}X}{\mathrm{d}t} = F(X) - G(X,Y) \tag{6a}$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \eta G(X,Y) - H(Y)\,, \tag{6b}$$

in which F is a function denoting the growth of prey, G is a function denoting the reduction of prey due to predation by Y, η is a yield factor coupling prey losses to predator gains, and H is a function determining the predator starvation rate in the absence of prey. The latter term is often called the maintenance energy term (Nisbet et al. 1983). The very simplest form the Lotka–Volterra system can take is

$$\frac{\mathrm{d}X}{\mathrm{d}t} = fX - gXY \tag{7a}$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \eta gXY - hY\,, \tag{7b}$$

with f, g and h constants. The interpretation of these equations is the following. Prey has a constant relative growth rate, and therefore grows exponentially in the absence of predators. Conversely, predators starve at a constant relative rate, leading to exponential decay of predator numbers in the absence of prey. The predation rate is modelled as proportional to the number of predator–prey encounters, and is thus proportional to the product of predator and prey numbers. Setting the right-hand sides of Eqs. 7a,b to zero yields a non-trivial equilibrium point of $X = h/(\eta g)$ and $Y = f/g$. This equilibrium is neutrally stable: any deviation from this point does not result in the system returning to the equilibrium, but in predator–prey oscillations of an amplitude depending on the initial deviation from equilibrium.

Despite the simplicity of the model, it already explains the existence of oscillations in the populations of predators and prey. Having said that, Eqs. 7a,b suffer from many shortcomings. The most glaring is the fact that the prey species will grow to infinity if predators are absent. This can be corrected by using logistic growth to model the prey, i.e.

$$F(X) = rX\left(1 - \frac{X}{K}\right)\,, \tag{8}$$

in which r is the maximum relative growth rate and K the carrying capacity of the ecosystem. The equilibrium position for X remains the same, but for Y we have

$$Y = \frac{r}{g}\left(1 - \frac{X}{K}\right)\,, \tag{9}$$

which is now a function of X. The equilibrium point is now found by intersecting the two zero-isoclines, in this case inserting the equilibrium

position of X in Eq. 9. This means that at equilibrium, we have $Y = r(1 - h/(\eta gK))/g$. In this case the equilibrium is stable: any deviation from equilibrium results in damped oscillations, and the system slowly returns to equilibrium.

Curiously, the above improvement does not explain the persistent predator–prey oscillations observed in nature. This is due to the other main shortcoming of Eqs. 7a,b, which is that the relative growth rate of the predators will go to infinity as the number of prey increases. In reality, predator growth rate is limited by various other factors, the most obvious of which are the maximal fecundity of the predator and the "handling time", which is the time needed to process the prey, during which the predator generally cannot attack another prey item. Improvements to Eqs. 7a,b are given in the following subsections, focussing on microbial predator–prey systems. Note that although the Lotka–Volterra equation was intended to model predator–prey systems, it has also been used to model mutualistic interactions between species (Neuhauser and Fargione 2004).

3.1 Improvements to the Predator Model

The improvements to the predator model focus on G, rather than on H, which is usually modelled as a constant starvation rate. As in the case of simple exponential (or Malthusian) growth for the prey, some saturation of the predator growth rate, and therefore of predation, is required. The Holling type II (Holling 1959) model is given by

$$G(X,Y) = \frac{gXY}{k_1 + X}\,, \tag{10}$$

in which k_1 is a saturation constant. It is based on the notion that any predator will spend some time processing the prey after having encountered it. The Holling type II model is essentially the same as the Monod model for bacterial growth (Monod 1950). If prey densities are high, the predator grows at a maximum relative growth rate g, whereas at low prey densities G approximates the Lotka–Volterra model, asymptotically approaching gXY/k as X approaches zero.

The Holling type II model shows several changes in the dynamical behaviour of the predator–prey system as compared to the Lotka–Volterra system with logistic growth of the prey. In this case the zero-isocline for the prey is a parabola, and depending on where the zero-isocline for the predator intersects it, the result may be locally stable, neutrally stable, or unstable (e.g. DeAngelis 1992). Thus, this system can explain many of the features in real predator–prey systems. This is shown in a hypothetical predator–prey system in Fig. 1. In this system, prey dynamics are modelled by logistic growth with $r = 0.2$ and a variable value of K. The Holling type II model

is used for the predator–prey interaction, with $g = 0.2$ and $k_1 = 5$; predator parameters are $\eta = 0.25$, and starvation rate $h = 0.02$. Figure 1a,c plots the predator–prey dynamics for $K = 10$. In this case the system is stable, because the (linear) predator isocline intersects the prey isocline after the maximum of the parabola, as shown in Fig. 1c. Even if the system is released from a point quite far from equilibrium, the system converges to the point of intersection of the isoclines. In Fig. 1b and d where $K = 20$, we see strong oscillations. In this case, the intersection of the isoclines lies before the maximum in the prey isocline, and even if the system is released very close to equilibrium the system veers away from it, finally approaching a stable limit cycle.

Numerous variants have been proposed (for a discussion see, e.g., DeAngelis 1992, pp 81–87). The Holling type III (Holling 1959) model is given by

$$G(X,Y) = \frac{gX^2Y}{k_1 + X^2}\,. \tag{11}$$

In this case, the saturation behaviour is as in Eq. 10, but the behaviour at low prey densities becomes quadratic, rather than linear, in the number of prey: as X approaches zero, G approaches gX^2Y/k. This models the difficulty predators may have in finding prey at lower densities, or the fact that any remaining prey may be harder to detect. Jost et al. (1973) proposed a variant of this

$$G(X,Y) = \frac{gX^2Y}{\left(k_1 + X\right)\left(k_2 + X\right)}\,, \tag{12}$$

with k_1 and k_2 saturation constants, which has similar behaviour. The Holling type III form appears to model vertebrate predators better than insects (DeAngelis 1992, pp 81–87) or microbes (Canale 1969; Kooi and Kooijmans 1994a), which are often modelled by the Holling type II model. The model of Jost et al. (1973) was also proposed in the context of a microbial ecosystem.

Another effect that may occur is that of interference (Arditi et al. 2004; Beddington 1975; DeAngelis et al. 1975; Hassel and Varley 1969), i.e. at high predator densities the efficiency of the predator declines, not because of plummeting prey numbers, but through predator–predator interactions. In all the above models G is a linear function of Y. This means that the *relative* predation rate is independent of Y. To include interference we should introduce a non-linear term to replace the linear one. Based on observations, Hassel and Varley (1969) propose the following modification of the standard Lotka–Volterra form

$$G(X,Y) = gXY^{1-m}\,, \tag{13}$$

which becomes

$$G(X,Y) = \frac{gXY^{1-m}}{k_1 + Y^{-m}X}, \tag{14}$$

in the Holling type II case (Arditi and Akçakaya 1990). Strictly speaking we should replace Y^{-m} by $(Y/Y_0)^{-m}$, with Y_0 the predator density corresponding to a single predator in the entire ecosystem (Arditi et al. 2004). If m is zero, we have no interference, whereas if m is negative we have co-operation. The interference parameter m can readily be determined empirically. Both equations are essentially empirical, so interpretation of the meaning of m is difficult. Beddington (1975) uses a behavioural argument to introduce a different form of interference

$$G(X,Y) = \frac{gXY}{k_1 + X + k_2(Y - Y_0)}, \tag{15}$$

by arguing that predators will lose some time in predator–predator encounters. In essence, this is a form of competitive inhibition, with k_1 the saturation constant as before, and k_2 the inhibition constant. DeAngelis et al. (1975) derive a very similar equation, in which Y_0 is omitted. In practice there is no difference between the two. It is often assumed that both forms of interference tend to damp out oscillations and increase the stability of the ecosystem, but recent analysis by Arditi et al. (2004) shows that this may not be the case for high interference levels if exponential growth of the prey is assumed (it remains stable if logistic growth is used). This effect can be seen in Fig. 2.

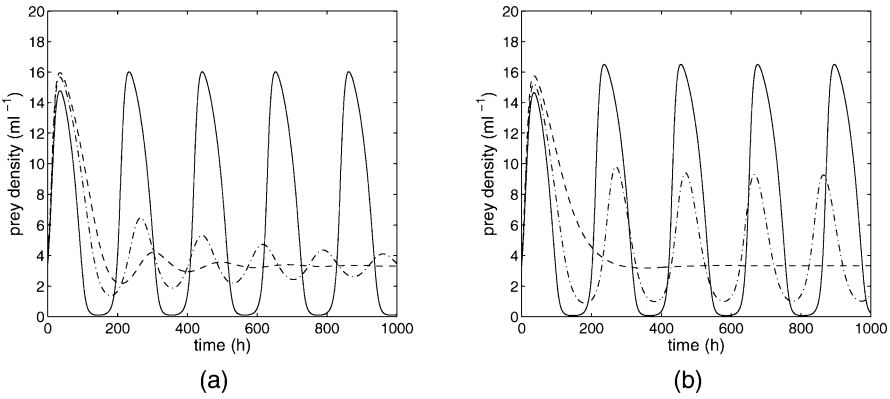

Fig. 2 Stabilizing effect on prey oscillations in the same system as in Fig. 1b but with mutual interference among predators: **a** according to model of Hassel and Varley (1969) with $m = 0.01$ (*solid line*), $m = 0.04$ (*dash-dot line*) and $m = 0.05$ (*dashed line*); **b** according to model of Beddington (1975) and DeAngelis et al. (1975) with $k_2 = 1$ (*solid line*), $k_2 = 5$ (*dash dot line*), and $k_2 = 10$ (*dashed line*). Whatever the model, the system is stabilized by mutual interference

Here the unstable system of Fig. 1b,d is used to show the stabilizing effect. In Fig. 2a the Hassel and Varley model is shown (only prey oscillations) for $m = 0.01$, 0.04 and 0.05. In Fig. 2b the model of Beddington (1975) and DeAngelis et al. (1975) is used for $k_2 = 1$, 5 and 10. In either case increasing the interference parameter increases stability.

3.2
Improvements to the Prey Model in the Microbial Case

As mentioned before, logistic growth is often used to model the prey dynamics. Though generally thought to be suitable for macroscopic prey, for microbes the Monod model is more suitable (Monod 1950; Koch 1998). In the following we assume the predator–prey system is contained within a chemostat with dilution rate constant D. Assuming that X_0 denotes the limiting substrate concentration, X_1 the prey concentration and S the concentration of substrate in the inflowing fluid, the set of differential equations becomes

$$\frac{\mathrm{d}X_0}{\mathrm{d}t} = D(S - X_0) - V_1 \frac{X_0}{K_1 + X_0} X_1 \tag{16a}$$

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = \mu_1 \frac{X_0}{K_1 + X_0} X_1 - DX_1 - G(X_1, Y) \tag{16b}$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \eta G(X_1, Y) - H(Y) - DY\,, \tag{16c}$$

with μ_1 the maximum specific relative growth rate, K_1 the saturation constant and V_1 the maximum specific uptake rate of X_0 by X_1. In the absence of predators, growth of the prey must precisely balance the dilution term DX_1, and the equilibrium concentrations of X_0 and X_1 become

$$X_0 = \frac{DK_1}{\mu_1 - D} \tag{17a}$$

$$X_1 = \frac{\mu_1}{V_1}\left(S - \frac{DK_1}{\mu_1 - D}\right)\,. \tag{17b}$$

Curiously, the equilibrium concentration of food is not a function of S, whereas the equilibrium concentration of the prey is a linear function of S. Note that this is only meaningful if

1. $\mu_1 > D$, otherwise X_0 is negative at equilibrium.
2. $DK_1/(\mu_1 - D) < S$, or else X_1 is zero or negative at equilibrium.

The first condition means that the bacterium must be able to grow at more than the dilution rate, the second that sufficient food must be available for it to grow at precisely the dilution rate.

Since Monod, many people have put forward improvements to Eqs. 16a,b. One objection that has been raised against this is that no maintenance en-

ergy term similar to $H(Y)$ in Eq. 6b is used (Nisbet et al. 1983), but this can either be assimilated into D, or added explicitly as an extra term. In some cases, multiple pathways for uptake of the same substrate are present, e.g. for low and high substrate availability, and this can be accommodated by multiple Monod terms, each with its own μ_i and K_i (Gerritse et al. 1992). Gerritse et al. (1992) also provide a model for aerobic and anaerobic behaviour, which was extended and used by Kamerman and Wilkinson (2002) and by Wilkinson (2002). A further refinement is that of a cascade of enzymes, or transporter protein mediated reactions which limit growth (Button 1991; Koch 1982). Many models also focus on the physiology of slow growth, which can be of particular importance in low-nutrient environments such as lakes (Button 1991, 1993; Koch 1997). On the other side of the spectrum we have substrate inhibition models (e.g. Tan et al. 1996), which deal with situations in which there is a sudden glut of food. A number of alternatives to the Monod equation are reviewed by Koch (1998), in which not only enzyme-mediated steps are considered, but also diffusion processes. Koch (1998) concludes that, while there are many shortcomings to the Monod model, it does describe the overall behaviour of bacteria growing in chemostats quite well, and (with caveats) can serve as a basis for qualitative and even quantitative modelling of bacterial growth. Especially when designing strategic models of microbial dynamics, its use seems justified (Gottschal 1993; Kooi and Kooijmans 1994a; Wilkinson 2001, 2002). This is why I will use the simple Monod model for prey throughout the rest of this chapter.

3.3 Modelling a Microbial Predator–Prey System

An early model for a microbial predator–prey system was put forward by Canale (1969). He used the Monod/Holling type II model for growth of both predator and prey. When modelling predatory bacteria or protozoa, maintenance energy must be taken into account (Nisbet et al. 1983), but not in the case of bacteriophages. Therefore, the growth of microbial predators Y on prey species X_1 is modelled as

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \frac{\mu_y X_1}{K_X + X_1} Y - (D + d_y) Y \,, \tag{18}$$

in which μ_y is the maximum specific growth rate, K_X is the saturation constant, D is the dilution rate of the chemostat, and d_y is the starvation rate. The differential equation for species X_1 is

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = \frac{\mu_1 X_0}{K_1 + X_0} X_1 - \frac{V_y X_1}{K_X + X_1} Y - D X_1 \,. \tag{19}$$

in which V_y is the maximum specific uptake rate of prey by predator. The differential equation for the limiting substrate becomes

$$\frac{\mathrm{d}X_0}{\mathrm{d}t} = D\left(S - X_0\right) - V_1 \frac{X_0}{K_1 + X_0} X_1 \,, \tag{20}$$

as before.

The behaviour of the set of ODEs defined by Eqs. 18–20 is similar to that of the logistic growth/Holling type II model shown in Fig. 1. This can be shown by stability analysis (Wilkinson 2001). Four different "phases" of the system can be identified (Kooi and Kooijman 1994a): (0) total washout of both species; (I) stable prey population with washout of predator; (II) stable coexistence of predator and prey, and (III) unstable coexistence (limit cycle behaviour). Levin et al. (1977) split phase III into two subphases: (IIIa) in which the limit cycle is itself stable (neither species is driven to extinction), and (IIIb) in which either the predator or both species are driven to extinction by increasing oscillations. The boundaries between these two subphases were determined by numerical analysis (Levin et al. 1977). In phases II and III, where predator and prey coexist, we can assume that all concentrations are non-zero, and we find the equilibrium point by equating the right-hand sides of Eqs. 18 and 20 to zero. A little algebra yields:

$$X_0 = \frac{1}{2}\left(S - K_1 - \frac{V_1 K_X}{\mu_y - D - d_y} \pm \sqrt{\left(S - K_1 - \frac{V_1 K_X}{\mu_y - D - d_y}\right)^2 + 4K_1 S}\right) \tag{21a}$$

$$X_1 = \frac{\left(D + d_y\right) K_X}{\mu_y - D - d_y} \tag{21b}$$

$$Y = \frac{D}{D + d_y} \frac{\mu_y}{V_y} \left(\frac{\mu_1}{V_1}\left(S - X_0\right) - X_1\right) \,. \tag{21c}$$

Thus it can be seen that the equilibrium concentration of prey is directly proportional to saturation constant K_X. The boundaries between the phases 0, I and II as a function of the chemostat's control parameters (dilution rate D and input concentration of the limiting substrate S) can be obtained analytically (Wilkinson 2001), whereas the boundary between phases II and III was obtained by local stability analysis of the steady-state solution. All boundaries are shown in Fig. 3b. Figure 3a shows the transient behaviour of the system using parameter values from Nisbet et al. (1983) and Kooi and Kooijman (1994a) (i.e. $K_1 = 8\,\mathrm{mg\,l^{-1}}$, $K_X = 9\,\mathrm{mg\,l^{-1}}$, $\mu_1 = 0.5\,\mathrm{h^{-1}}$, $\mu_y = 0.2\,\mathrm{h^{-1}}$, $V_1 = 1.25\,\mathrm{h^{-1}}$ and $V_y = 0.3333\,\mathrm{h^{-1}}$). Note that in all these studies the inflowing substrate levels are held constant. If they fluctuate, the dynamics become more complicated, allowing multiple prey species to coexist on a single limiting substrate (Grover 1988, 1990).

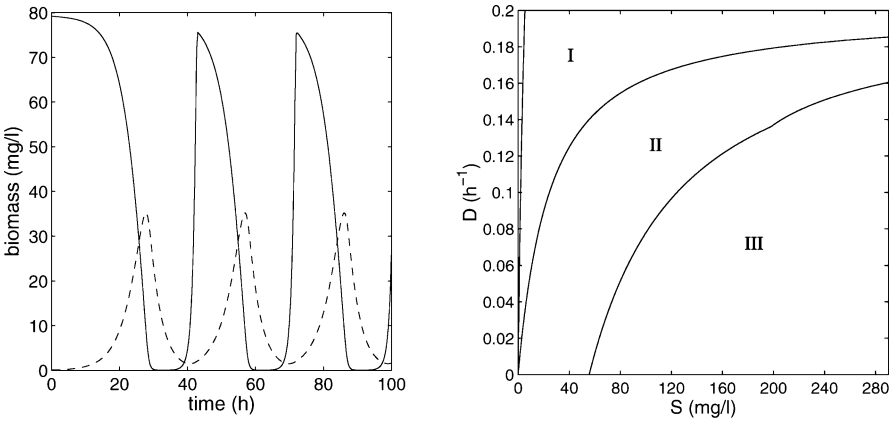

Fig. 3 Phase boundaries and transient behaviour of microbial predator–prey system described by Eqs. 18–20, with parameter settings according to Nisbet et al. (1983), i.e. $K_1 = 8\,\mathrm{mg\,l^{-1}}$, $K_X = 9\,\mathrm{mg\,l^{-1}}$, $\mu_1 = 0.5\,\mathrm{h^{-1}}$, $\mu_y = 0.2\,\mathrm{h^{-1}}$, $V_1 = 1.25\,\mathrm{h^{-1}}$ and $V_y = 0.3333\,\mathrm{h^{-1}}$. **a** Transient behaviour showing strong predator (*dashed line*)–prey (*solid line*) oscillations; **b** boundaries between phases as a function of dilution rate D and inflowing substrate concentration S. Note how the probability for oscillations increases with enrichment of the ecosystem. See text for details

3.4 Modelling Bacterium–Phage Systems

Bacterium–phage systems in chemostats have long been studied as "ideal" predator–prey systems, due to their small scale and short generation time (Campbell 1961; Chao et al. 1977; Levin et al. 1977; Bohannan and Lenski 1997; Weld et al 2004). Because the phage life cycle is similar to the life cycle of *Bdellovibrio* and similar organisms, I will present the methods used to model phages before describing predatory prokaryotes proper. All the work cited above uses DDEs to model a phage's life cycle using a single delay τ, which is the time between invasion and phage release. Following Levin et al. (1977), rather than Campbell (1961) who uses logistic prey growth, we use Monod growth as before. Note that the predator can be in two phases: the free and the reproductive phase within the infected host. Let X_1 be the prey as before; Y_{free} denotes the free predators and $[X_1\,Y]$ denotes the complex formed when prey is bound to predator (the infected bacteria). Furthermore, assume the rate of *productive* collisions (i.e. which result in prey capture or penetration) between predator and prey is r per unit of prey species, per unit of predator. Note that the actual collision rate may be larger by an order of magnitude or more. The prey/predator complex dissociates after a time delay τ, yielding $y_x + 1$ new predators. Because one predator is lost in the infection, we have

a net yield of y_x. We now obtain

$$\frac{dX_0}{dt} = D(S - X_0) - V_1 \frac{X_0}{K_1 + X_0}\left(X_1 + [X_1 Y]\right) \tag{22a}$$

$$\frac{dX_1}{dt} = \frac{\mu_1 X_0}{K_1 + X_0} X_1 - rY_{\text{free}} X_1 - DX_1 \tag{22b}$$

$$\frac{dY_{\text{free}}}{dt} = (y_x + 1)e^{-D\tau} X_1' Y' - rX_1 Y_{\text{free}} - DY_{\text{free}} \tag{22c}$$

$$\frac{d[X_1 Y]}{dt} = -e^{-D\tau} X_1' Y' - D[X_1 Y] + rX_1 Y_{\text{free}}\,, \tag{22d}$$

in which X_1' and Y' denote the density of X_1 and Y at time $t - \tau$, respectively. Note that it is assumed that infected prey also use the substrate. The term $e^{-D\tau} X_1' Y'$ denotes the amount of $[X_1 Y]$ which formed at $t - \tau$, and has not yet been washed out of the chemostat. In the last term in Eq. 22a, the factor $(X_1 + [X_1 Y])$ means that the complex $[X_1 Y]$ consumes substrate, which may be partly right for phage-infected prey, but much less for *Bdellovibrio*-infected prey.

Approximations using (slightly more tractable) ODEs have also been proposed. Payne and Jansen (2001) transform the time delay τ into a lysis rate $k_1 = 1/\tau$. In this case we obtain the set of ODEs

$$\frac{dX_0}{dt} = D\big(S - X_0\big) - V_1 \frac{X_0}{K_1 + X_0}\big(X_1 + [X_1 Y]\big) \tag{23a}$$

$$\frac{dX_1}{dt} = \frac{\mu_1 X_0}{K_1 + X_0} X_1 - rY_{\text{free}} X_1 - DX_1 \tag{23b}$$

$$\frac{dY_{\text{free}}}{dt} = \big(y_x + 1\big)\, k_1\, [X_1 Y] - rX_1 Y_{\text{free}} - DY_{\text{free}} \tag{23c}$$

$$\frac{d[X_1 Y]}{dt} = -k_1 [X_1 Y] - D![X_1 Y] + rX_1 Y_{\text{free}}\,. \tag{23d}$$

Figure 4 shows the result of a simulation using both models for an *E. coli*–T2 phage system, using the parameters from Levin et al. (1977). The overall behaviour of both models is similar, though the ODE method tends to overestimate predator growth (Weld et al. 2004). Another small difference is the slightly later onset of the oscillations in the case of the DDE approach. Many variants of the DDE method have been proposed, and the interested reader is referred to Weld et al. (2004).

3.5 Modelling Predatory Prokaryotes

To model prokaryote predators we must of course start with an understanding of how they attack and consume their prey. Martin (2002) distinguishes four types of predatory prokaryotes (in reverse order compared to Martin):

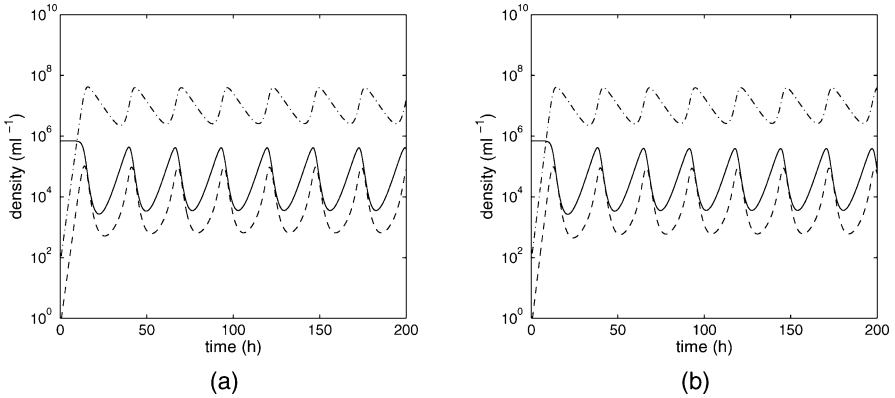

Fig. 4 DDE vs. ODE models for *E. coli*–T2 phage systems, showing prey density (*solid line*), infected prey density (*dotted line*) and phage density (*dash-dot line*). **a** DDE model according to Levin et al. (1977); **b** ODE equivalent according to Payne and Jansen (2001). The chief difference is a slight delay in the onset of oscillations in the DDE case

(1) periplasmic, in which the predator invades the periplasmic space of Gram-negative cells as in the case of *Bdellovibrio* and *Bacteriovorax* species; (2) direct invasion into the cytoplasm as in *Daptobacter* (Guerrero et al. 1986); (3) epibiotic, i.e. attached to the surface such as done by *Vampirococcus*; and (4) the "wolf-pack" approach, in which no physical contact is needed, but the predatory bacteria release lytic substances which break down the prey, as seen in *Myxococcus* (Burnham et al 1981), *Lysobacter* (Lin and McBride 1996) and *Pseudomonas* strain 679-2 (Casida and Lukezic 1992; Cain et al. 2003). The last case may be considered a simple extension of the production of lytic bacteriocins, which is very common amongst bacteria (Chao and Levin 1981; Frank 1994; Riley and Gordon 1996; Iwasa et al. 1998). By simply absorbing the nutrients released by the destruction of competitors, all these bacteria could be considered non-obligately predatory prokaryotes (see the chapter by Jurkevitch and Davidov, this volume).

From the point of view of modelling, the first two types of predator are identical, because the model simply does not take the location of the predator within the cell into account. The third and fourth are slightly different, because multiple organisms may attack a single host (Esteve and Gaju 1999; Guerrero et al. 1986; Martin 2002). The mechanisms are slightly different and I will propose two different models for types (3) and (4) in the following subsection.

We must also make the distinction between obligate and non-obligate predators. The former can be modelled with a single substrate uptake process, whereas the latter requires two: one for the predatory mode and one for the non-predatory mode. Furthermore, we need to model a switch between these modes. This is discussed in Sect. 3.5.2.

3.5.1 Obligate Predators

We will start by modelling the best-known obligately predatory prokaryote: *B. bacteriovorus*. Given that the lifestyle of *B. bacteriovorus* is similar to that of phages, the approach to phage modelling can be applied to *B. bacteriovorus*, as was done by Marchand and Gabignon (1981) and Dulos and Marchand (1984). They also used a DDE, similar to that of Levin et al. (1977), but with some simplifications. First of all they used exponential growth for the prey, without taking its substrate into account, which is an oversimplification. Secondly, the flush-out term $e^{-D\tau}$ was not included. This can be defended for low dilution rate D combined with a fairly small delay time τ. Dulos and Marchand (1984) used $D = 0.03\,\mathrm{h}^{-1}$ and $\tau = 3\,\mathrm{h}$, which means that $e^{-D\tau} = 0.9131$. Given the many inaccuracies in the measurements, this may be close enough to unity. Their set of coupled DDEs is

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = \mu X_1 - rY_{\mathrm{free}}X_1 - DX_1 \tag{24a}$$

$$\frac{\mathrm{d}Y_{\mathrm{free}}}{\mathrm{d}t} = \left(y_x + 1\right) X_1' Y' - r\left(X_1 + [X_1 Y]\right) Y_{\mathrm{free}} - DY_{\mathrm{free}} \tag{24b}$$

$$\frac{\mathrm{d}\,[X_1 Y]}{\mathrm{d}t} = -X_1' Y' - D\,[X_1 Y] + rX_1 Y_{\mathrm{free}}\,, \tag{24c}$$

with μ the relative growth rate of prey. Note that multiple invasion is modelled in Eq. 24b by the additional $r[X_1 Y]Y_{\mathrm{free}}$ term. Though it is not apparent in this set of equations, Dulos and Marchand do model the starvation of free predators in their simulation program. They note the difficulty in modelling the starvation of those predators *who have not found a prey within the starvation time* $\tau_1 = 10\,\mathrm{h}$ within the framework of DDEs or ODEs. The reason for this is that the effect depends on the age structure of the free predator population. Ideally, this should be modelled through partial differential equations similar to the dynamic energy budget model (Kooijman 1993; Kooi and Kooijman 1994a,b). The approach in Dulos and Marchand (1984) is similar in that it effectively discretizes the age distribution of free prey, and transforms the problem back into a more complicated ODE, which they solve with a Euler approach with a fixed (20 min) time step. The predator can be modelled by an array of variables, each representing an age class. At each time step, we can first compute how many of each class find prey, and put any remaining predators in a higher age class. All new predators are put in the lowest class.

Following Dulos and Marchand's parameter settings we have $\tau = 1/k_1 \cong 3.0\,\mathrm{h}$. This system is shown in Fig. 5a, in which $\mu = 0.06\,\mathrm{h}^{-1}$, $y_x = 8$, $D = 0.03\,\mathrm{h}^{-1}$, $r = 3 \times 10^{-9}\,\mathrm{ml}^{-1}\,\mathrm{h}^{-1}$ and $k_1 = 1/3.0\,\mathrm{h}^{-1}$. The initial prey and predator densities are $3 \times 10^6\,\mathrm{ml}^{-1}$ and $10^7\,\mathrm{ml}^{-1}$, respectively. As can be seen the

oscillations increase in amplitude until one or both species go extinct. Figure 5b shows the effect of ignoring starvation, leading to more regular oscillations. We compare this to the DDE approach of Levin et al. (1977) with added starvation and similar parameter settings, but additionally $\mu_1 = V_1 = 1\,\mathrm{h}^{-1}$, $S = 3 \times 10^6\,\mathrm{ml}^{-1}$ and $K_1 = 10^6\,\mathrm{ml}^{-1}$ (note that the latter two are expressed in equivalent number of prey bacteria per millilitre), shown in Fig. 5c. Somewhat surprisingly, the change in prey model to a Monod-type substrate limited growth stabilizes the system dramatically. Only by raising r to $3 \times 10^{-8}\,\mathrm{ml}^{-1}\,\mathrm{h}^{-1}$ do we get any oscillations, as seen in Fig. 5d. If we follow the ODE approach and assume that the dilution rate constant D is small compared to the reaction constants, we can approximate this set as follows by so-called quasi-steady-state analysis. We assume that the prey capture and predator division reactions are fast enough to settle into equilibrium. At

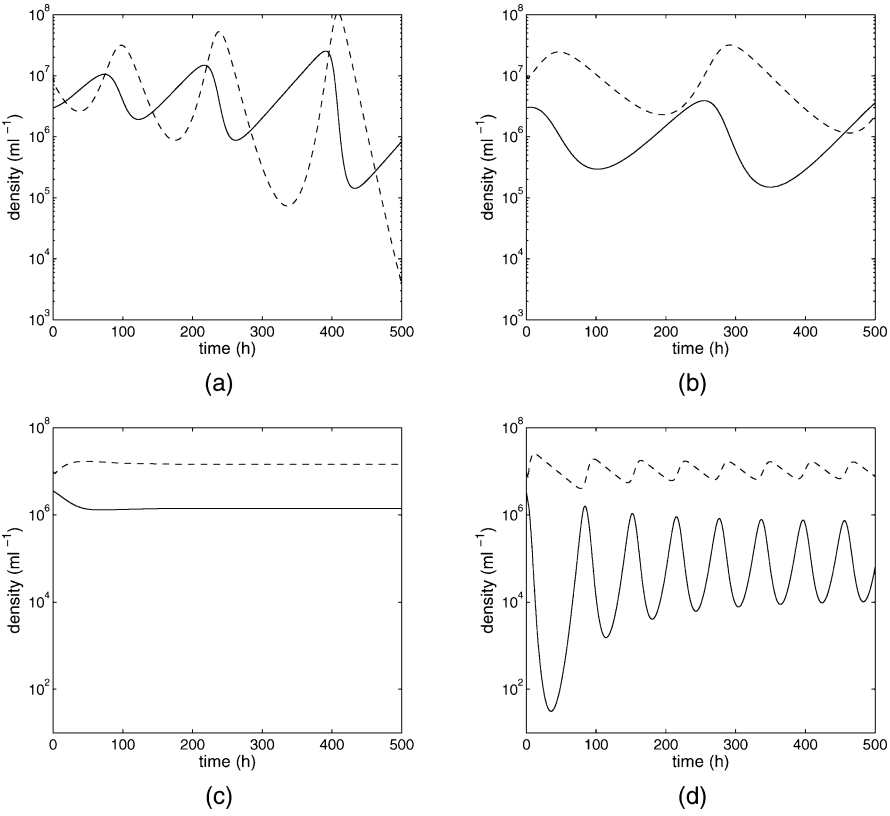

Fig. 5 Different models for the *B. bacteriovorus* (*dashed line*)–*E. coli* (*solid line*) system. **a** DDE according to Dulos and Marchand (1984); **b** same as **a** but ignoring starvation; **c** DDE according to Levin et al. (1977) with the same parameter settings as **a**; **d** only by increasing collision rate r by a factor of 10 do oscillations occur

(quasi-)steady state we have

$$[X_1 Y] = \frac{r}{k_1} X_1 Y_{\text{free}} ;$$

inserting this in Eqs. 23c,d and summing we arrive at

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = y_x k_1 \frac{X_1}{k_1/r + X_1} Y , \tag{25}$$

which is just the Holling type II model (Holling 1959). Whether quasi-steady-state analysis is justified depends very much on the situation. The same simulation as in Fig. 6a using the explicit form of Eqs. 22a–d was performed using the Holling type II approximation. The results are shown in Fig. 6b. Clearly, at a dilution rate of $D = 0.03\,\mathrm{h}^{-1}$, the Holling approximation is quite reasonable. This is not unexpected because the time constant k_1 is an order of magnitude larger than the dilution rate.

For epibiotic predatory bacteria, such as *Vampirococcus* spp., which attach to the outside and feed there, the Holling type II model is probably justified. In this case, multiple predator cells might attach to a single prey item (although this is not necessarily the case for all epibiotic interactions). This situation is more or less similar to "normal" feeding by bacteria, which is generally modelled through the use of Monod models, which are functionally identical to the Holling type II model. We can revert to the model given by Eqs. 18–20. Given the difficulties in culturing *Vampirococcus* in the laboratory (Martin 2002), no models have been put forward to date, so parameter estimation, let alone model validation, is difficult.

Finally, we have the wolf-pack type, which we can model using a combination of the model for bacteriocin production and susceptibility (Frank

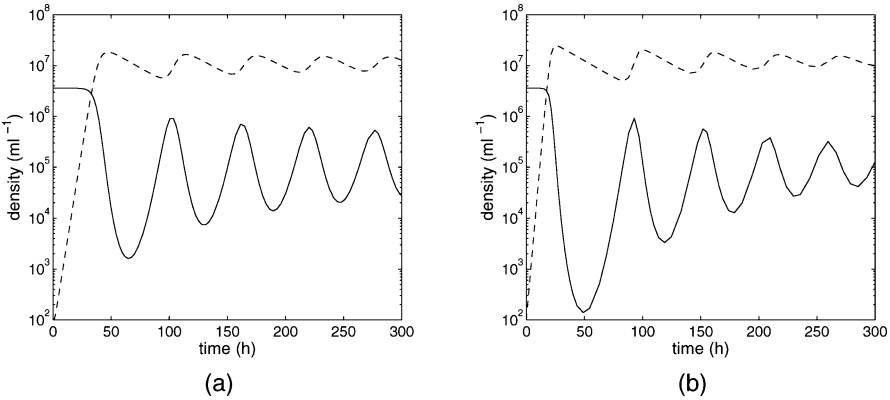

Fig. 6 Predator–prey oscillations in *Bdellovibrio*-type predator model. **a** Two curves are shown: prey density X_1 (*solid line*) and free predator density Y_{free} (*dashed line*). **b** The same model in a Holling type II approximation

1994; Wilkinson 2002), and allowing the predator to feed upon the materials released by lysis of the prey. The set of equations becomes somewhat more complex. Let T be a lytic toxin released by the predator Y. As before, we have the prey X_1 growing on X_0 through Monod kinetics. We assume the prey is destroyed at a rate proportional to the concentration of T. This reaction consumes some fraction of T. The destruction of X_1 by T leads to the formation of a substrate S_y on which Y grows directly, using Monod kinetics again. The set of differential equations becomes

$$\frac{\mathrm{d}X_0}{\mathrm{d}t} = D\left(S - X_0\right) - V_1 \frac{X_0}{K_1 + X_0} X_1 \tag{26a}$$

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = \frac{\mu_1 X_0}{K_1 + X_0} X_1 - \kappa T X_1 - D X_1 \tag{26b}$$

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \frac{\mu_y S_y}{K_S + S_y} Y - \left(D + d_y\right) Y \tag{26c}$$

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \alpha Y - \beta T X - D T \tag{26d}$$

$$\frac{\mathrm{d}S_y}{\mathrm{d}t} = \frac{V_y S_y}{K_S + S_y} Y - \eta \kappa T X - D S_y\,, \tag{26e}$$

with α, β and κ rate constants and η a conversion efficiency factor. For the sake of simplicity, we assume that the two substrates X_0 and S_y are different, which need not be the case. Rigorous analytical treatment of this set of ODEs is beyond the scope of this chapter. It may well be possible to simplify this set to a model similar to that of Eqs. 18–20, but this is not obvious. Preliminary numerical analysis suggests that Eqs. 26a–e resemble bacteriocin-mediated interactions in an important way. Bacteriocin-mediated interactions are bistable: either the susceptible species survives, or the producer species survives, but stable coexistence is impossible (Frank 1994; Wilkinson 2002). This is in part due to the positive feedback loop in this set of equations. This occurs because more predators means more toxin, means more substrate for the predators, means faster predator growth, etc. The reverse is also true: if predator numbers drop, so does the toxin level, and therefore substrate levels, meaning slower predator growth, etc. This means that once the predators, and therefore the toxin levels, have crossed a certain threshold, a runaway reaction takes place, killing all the prey. After this the predator population also collapses. In the alternative scenario, toxin levels are not high enough to kill enough prey, and the predator dies out. This means that if the predator is to be able to invade a system of only prey, it must produce a toxin potent enough to kill sufficient prey quickly, so that it can then grow at more than the dilution rate. Such potent toxins means that predators always wipe out the prey once their numbers start growing. This suggests that

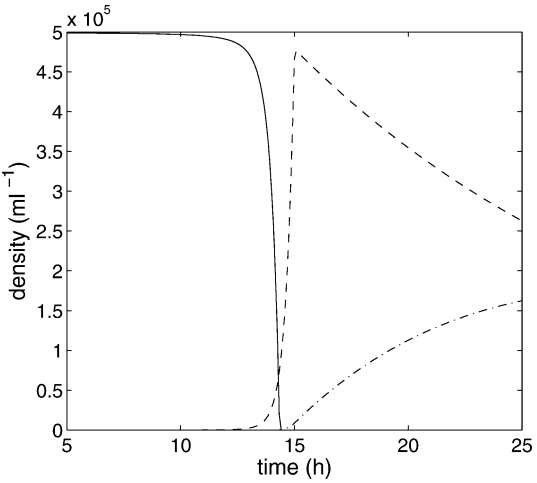

Fig. 7 A simulation for wolf-pack predators: prey (*solid line*), predator (*dashed line*) and toxin level (*dash-dot line*) are shown as a function of time. As predator numbers increase slowly, toxin levels rise gently so long as there are many prey to absorb the toxin. Once a certain threshold is reached, the prey kill rate outstrips the prey growth rate, leading to a collapse of the prey population, sudden release of substrate and an explosive growth of the predator, which then starves in the absence of prey

only predators that cannot invade pure prey systems might be able to coexist with prey.

We can conclude that, unless some damping mechanism is available, wolf-pack feeding does not appear to be stable. This suggests it will only occur in non-obligate predators, which is to some degree supported by observations (Martin 2002). A typical simulation run is shown in Fig. 7.

3.5.2 Non-Obligate Predators

Non-obligate predators may survive without prey, and in the prokaryote case often only switch to predatory behaviour under conditions of low substrate availability (Esteve and Gaju 1999; Guerrero et al. 1986; Martin 2002). Though *B. bacteriovorus* is probably the best-known predatory prokaryote, non-obligate predatory behaviour may actually be more common than obligate predatory behaviour. Modelling a non-obligate predator can be done by combining the standard Monod model for growth on regular substrate with, e.g., the Holling type II model for the predator phase. If the predatory behaviour only switches on below some minimum substrate level $S_{\min}$, we also need to model a switch function T. This function is zero at low substrate level, and switches rapidly, but preferably continuously, to 1 above $S_{\min}$. One

plausible model would be

$$T(S) = \frac{S^n}{S_{\min}^n + S^n} .$$

If n is larger than 1, this is a sigmoid function which switches rapidly from zero to 1 around $S_{\min}$, as is shown in Fig. 8 for various values of n. The equation for growth of a non-obligate predator then becomes

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = T(S)\mu_{\max}\frac{SY}{K_S + S} + \big(1 - T(S)\big)\,\mu_y\frac{X_1 Y}{K_X + Y} , \tag{27}$$

and for the prey (X_1 growing on X_0) we obtain

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = \mu_1\frac{X_0 X_1}{K_1 + X_0} - \big(1 - T(S)\big)\,V_y\frac{X_1 Y}{K_X + Y} , \tag{28}$$

disregarding the dilution of the chemostat for the moment.

An alternative to this approach would be to model the predator not by one, but by two variables, Y_1 denoting the non-predatory mode and Y_2 the predatory mode. In this case, we must model the transfer rate from predatory to non-predatory mode in some way. Let $\tau_{\max}$ be the maximum switch rate. The forward switching function T_{12} could then be modelled as

$$T_{12}(S) = \tau_{\max}\frac{S_{12}^n}{S_{12}^n + S^n} , \tag{29}$$

in which S_{12} is the substrate concentration at which half the maximum forward switch rate is achieved. Obviously, if $S \gg S_{12}$ the forward switch rate is

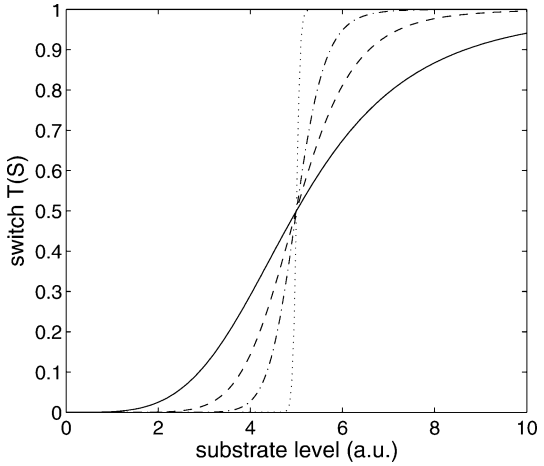

Fig. 8 The switch function $T(S)$ for $S_{\min} = 5$, and $n = 4$ (*solid line*), $n = 8$ (*dashed line*), $n = 16$ (*dash-dot line*) and $n = 128$ (*dotted line*). As n increases the sigmoidal shape progresses towards a more threshold-like behaviour. a.u.: arbitrary units

near zero. The reverse switch function T_{21} is modelled as

$$T_{21}(S) = \tau_{\max} \frac{S^n}{S_{21}^n + S^n}\,, \tag{30}$$

in which S_{21} is the concentration of S at which the reverse switch rate is half the maximum rate. It is possible to let the switch points be equal, i.e. $S_{12} = S_{21} = S_{\min}$. However, the above method is slightly more general. Assuming the offspring of Y_1 are also non-predatory and the offspring of Y_2 are all in predatory mode, the set of differential equations now becomes

$$\frac{\mathrm{d}Y_1}{\mathrm{d}t} = \mu_{\max} \frac{SY_1}{K_S + S} - T_{12}(S)Y_1 + T_{21}(S)Y_2 \tag{31a}$$

$$\frac{\mathrm{d}Y_2}{\mathrm{d}t} = \mu_y \frac{X_1 Y_2}{K_X + Y_2} + T_{12}(S)Y_1 - T_{21}(S)\,Y_2 \tag{31b}$$

$$\frac{\mathrm{d}X_1}{\mathrm{d}t} = \mu_1 \frac{X_0 X_1}{K_1 + X_0} - V_y \frac{X_1 Y_2}{K_X + Y_2}\,. \tag{31c}$$

Note that many other switch functions could be used instead. These equations just serve to show how such predators could be modelled. I am not aware that similar types of ODEs have ever been used to mathematically model any of the known non-obligate prokaryote predators. Though easy to draw up, and fairly straightforward to simulate by computer, these equations are not easy to analyse, and the large number of parameters makes it hard to estimate them.

3.6 Prey Countermeasures

Another feature that could be modelled mathematically is that of prey countermeasures. As observed by Shemesh and Jurkevitch (2004), some prey species apparently respond to predation by switching to a resistant phenotype, in a similar way as bacteria may switch to an antibiotic-resistant phenotype when challenged by antibiotics (Balaban et al. 2004). Leaving aside the case of mutants, we assume that this resistant phenotype incurs some growth penalty, as observed in the case of antibiotic resistance (Balaban et al. 2004). If this were not the case, mutants only ever expressing that phenotype would dominate the population once they appeared. A simple way to model this is to model the prey species by two variables: X_1 which is susceptible and X_1^* which is not. The latter grows at a slightly lower growth rate determined by parameters μ_1^* and K_1^*. We will first treat the case of "type I persisters", as defined by Balaban et al. (2004). A predator–prey collision can now result in two outcomes: (1) either the prey is penetrated by the predator as before, with probability $1 - p$, or (2) the predator swims away and the prey is triggered to switch to resistant mode, with some probability p. In type II persisters, the switch to the resistant phenotype occurs at a constant rate in-

dependently of any trigger (Balaban et al. 2004). In either case, the resistant phenotype switches back to the sensitive strain at some rate s_r. Of course, the reverse switch rate could also be made dependent on some trigger (e.g. absence of collisions during some time interval). We arrive at the following set of differential equations

$$\frac{dX_0}{dt} = D\left(S - X_0\right) - V_1 \frac{X_0}{K_1 + X_0} X_1 - V_1^* \frac{X_0}{K_1^* + X_0} X_1^* \tag{32a}$$

$$\frac{dX_1}{dt} = \frac{\mu_1 X_0}{K_1 + X_0} X_1 - \left(r Y_{\text{free}} + D\right) X_1 \tag{32b}$$

$$\frac{dX_1^*}{dt} = \frac{\mu_1^* X_0}{K_1^* + X_0} X_1^* + p r Y_{\text{free}} X_1 - \left(s_r + D\right) X_1^* \tag{32c}$$

$$\frac{dY_{\text{free}}}{dt} = \left(y_x + 1\right) k_1 \left[X_1 Y\right] - \left(\left(1 - p\right) r X_1 + D\right) Y_{\text{free}} \tag{32d}$$

$$\frac{d\left[X_1 Y\right]}{dt} = -\left(k_1 + D\right)\left[X_1 Y\right] + r X_1 Y_{\text{free}} \,. \tag{32e}$$

The complexity of this system makes analysis and estimation of parameters quite hard. Nonetheless, we can use this set of ODEs to obtain some feeling for the importance of the parameters. The results of a number of simulations are shown in Fig. 9. In Fig. 9a the same system as in Fig. 5d is shown, which is the starting point of our modifications. In Fig. 9b–d we have set $\mu_1^* = 0.99\mu_1$, $K_1^* = K_1$ and $p = 0.5$, whilst doubling the collision rate r to ensure the same number of *productive* collisions with Y_{free} takes place. In Fig. 9b we set the reverse switch rate $s_r = 0.06\mu_1$, corresponding to a switch rate about 1/16 times the fastest doubling time (Shemesh and Jurkevitch 2004); in Fig. 9c we have $s_r = 0.01\mu_1$. Clearly having a $p > 0$ increases the survival rate, as suggested by Shemesh and Jurkevitch (2004). Increasing p to increase the forward switching rate does not change the dynamics of the system dramatically, it just leads to a further reduction of predator numbers. Reducing the reverse switch rate delays the return of the original phenotype to dominance as expected. Note that setting the reverse switch rate s_r to (nearly) zero, and making the forward switch probability small, and possibly independent of collision with Y_{free}, allows modelling of a genotypical switch (mutation) such as that observed in an *E. coli* bacteriophage PP01 system (Mizoguchi et al. 2003), rather than a phenotypic response using essentially the same set of equations. This is shown in Fig. 9d where $p = 0.09$ and $s_r = 0$. It is difficult to see in the plot, but the sensitive strain does recover very slowly after elimination of the predator, due to its slight growth advantage, as suggested by (Shemesh and Jurkevitch 2004). In the case described by Mizoguchi et al. (2003), the phage apparently responded to the prey response by mutating itself, potentially starting (or simply continuing) an arms race.

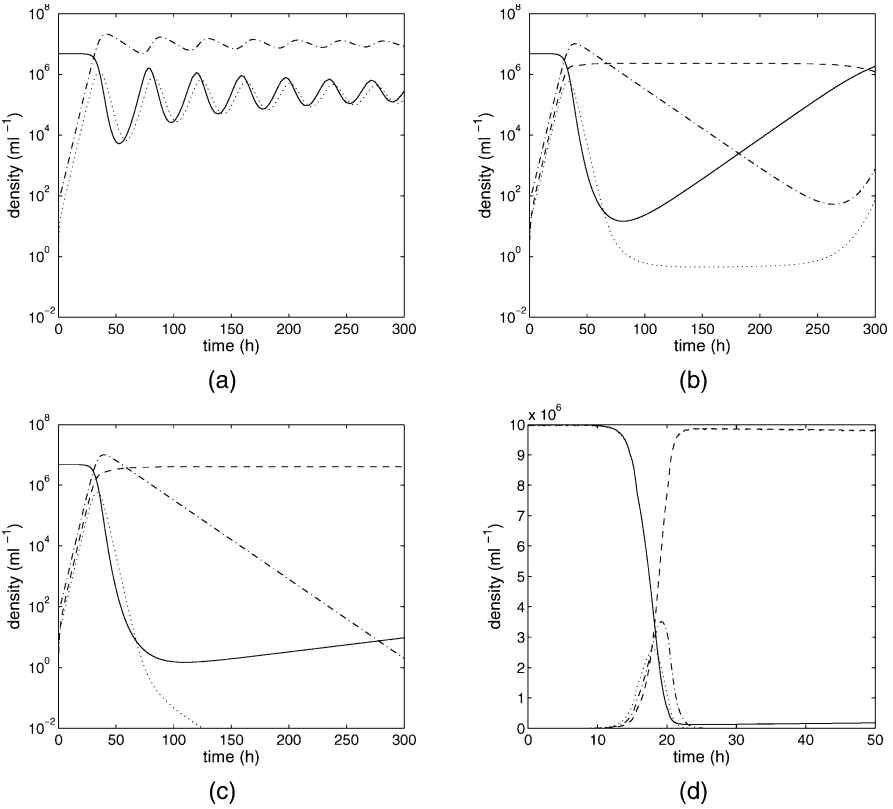

Fig. 9 Prey countermeasures by switching to a resistant state, showing susceptible state X_1 density (*solid line*), resistant state density X_1^* (*dashed line*), free predator density Y_{free} (*dash-dot line*), and bdelloplast density $[X_1 Y]$ (*dotted line*). **a** No countermeasure ($p = 0$); **b** prey switches to resistant mode after collision with Y_{free} with probability $p = 0.5$, collision rate r doubled with respect to **a**, and reverse switch rate $s_r = 0.06\mu_1$; **c** same as **b**, but with $s_r = 0.01\mu_1$; **d** $p = 0.09$ and $s_r = 0$, to mimic mutations rather than phenotypic switches

Equations 32a–e are only one way to model this type of countermeasure. If the switch is based on some active response by the prey, we could also model the signal transduction in the prey using density-dependent switches such as those in the model for non-obligate predators in Eqs. 31a–c. The effect described by Shemesh and Jurkevitch (2004) is by no means the only possible countermeasure. The prey species could also respond to predation by producing cidal or inhibitory toxins, such as bacteriocins. These could be modelled using the differential equations from Frank (1994) and Wilkinson (2002), similar to the lytic toxins used in Eqs. 26a–e. A further possibility is the production of decoys: objects which in some way distract the predator long enough to let the prey escape. This is similar to tail autotomy in certain

lizards (Dial and Fitzpatrick 1983), leg autotomy in arachnids (Punzo 1997) and the immune evasion strategies used by certain parasites (Donelson 1998; Ramasamy 1998). By casting off some part of the outer envelope, e.g. membrane vesicles (Beveridge 1999; Mashburn and Whiteley 2005), bacteria might be capable of something similar. The decoy effect is explained in detail in Sect. 4.2.

4 Third-Species Effects

Adding a third species to a system can have a profound effect, and just a few of the potential 704 different effects (Harmon and Andow 2002) will be discussed, in particular those which have been noted in a microbial context.

4.1 Alternative Prey

In the fields of control of potential pathogens in waste water (Mallory et al. 1983) and the control of insect pests (Harmon and Andrews 2002), the possibility of the so-called alternative prey model has been put forward. Before that it was also studied by Levin et al. (1977) in the setting of bacterium–phage systems. Suppose we wish to eliminate some pathogen X_1 in waste water by using predator Y. However, the levels of X_1 in the water may be too low to support the predator Y, let alone yield the predator–prey oscillations which would lead to a catastrophic collapse of the numbers of X_1. In this case the third, harmless species, X_2, is added to the water simultaneously with Y. This can enrich the ecosystem to the level that the "paradox of enrichment" effect takes place, i.e. the diversity reduces and ideally the pathogen disappears. The key issue is that the alternative prey effect occurs mainly in generalist predators, simply because true specialists do not have alternatives. Modelling this situation is straightforward. Simply add a third species X_2, which either grows on the same substrate as X_1 or on a different one, and add a second predation term to the model of the predator

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \frac{\mu_{y1} X_1}{K_{X1} + X_1} Y + \frac{\mu_{y2} X_2}{K_{X2} + X_2} Y - DY - d_y Y \,. \tag{33}$$

The results of the alternative prey effect depend on whether X_2 competes for the same substrate with X_1. If this is the case, X_1 is threatened both by increased predation and by competition. Nonetheless, X_1 could still eliminate X_2 provided it can grow faster than X_2. A few simulation runs using the same system as in Fig. 3 are shown in Fig. 10. Input substrate level S was lowered to $100\,\mathrm{mg\,l^{-1}}$ to obtain a stable predator–prey equilibrium. In all cases the

growth rate of X_2 is $0.99\mu_1$, to give it a slight disadvantage relative to X_1. Figure 10a,b concern the situation where X_2 is sustained by a separate substrate, i.e. it does not compete for X_0. In Fig. 10a the input level of the substrate for X_2 is equal to S, the input substrate level for X_1. Note the strong predator–prey oscillations, in which the levels of X_1 and X_2 are almost identical. The system behaves very much like the two-species system with double the amount of nutrients. In Fig. 10b the input substrate level for X_2 is $2S$, resulting in different predator–prey oscillations in which X_1 is suppressed more. In the case that X_1 and X_2 are in direct competition for the same resources the situation is very different, as shown in Fig. 10c,d. If X_2 is added at the equilibrium level of X_1, it fails to have any real impact, and the system will ultimately settle back

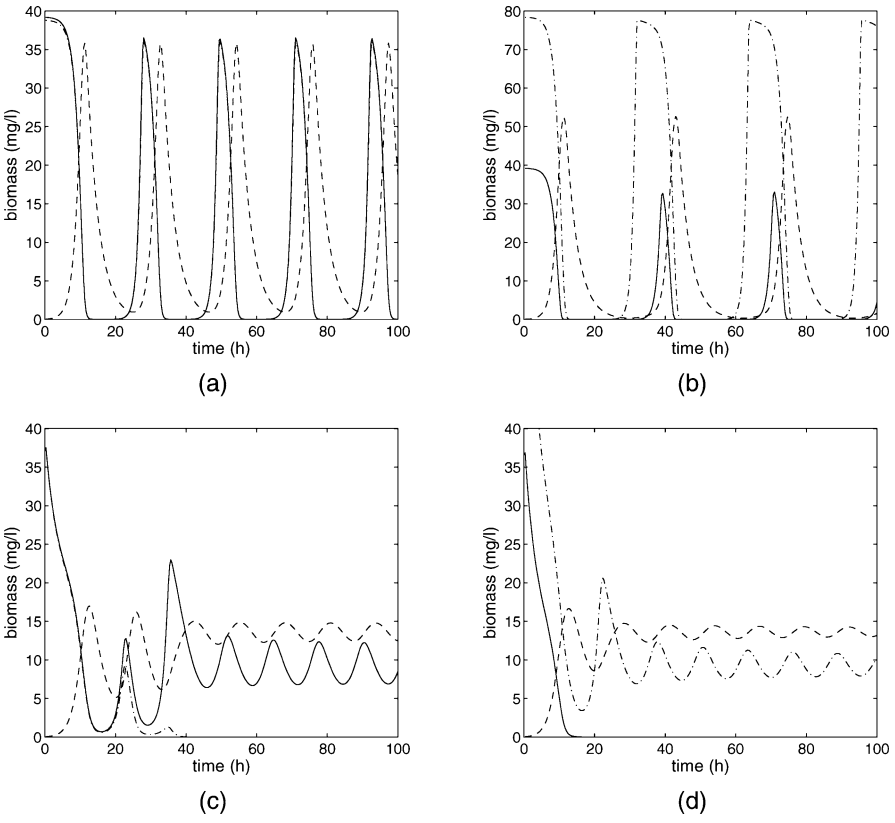

Fig. 10 Alternative prey effects in the same system as shown in Fig. 3. *Top row*: alternative prey X_2 (*dash-dot line*) that does not compete for the same substrate as regular prey X_1 (*solid line*): **a** equilibrium level (without predation) of X_2 equals that of X_1; **b** equilibrium level (without predation) of X_2 twice that of X_1. *Bottom row*: X_2 that does compete with X_1: **c** X_2 added at the same level as equilibrium of X_1; **d** X_2 added at twice the equilibrium level of X_1. Predator Y shown as *dashed line*

into equilibrium (Fig. 10c). However, if the initial density of X_2 is doubled, it leads to an eradication of X_1, despite the fact that the latter has a higher growth rate at identical substrate levels. The system now gradually converges to a two-species equilibrium of X_2 and Y (Fig. 10d). The mathematically interested reader is referred to Levin et al. (1977) and Deng et al. (2003) for a more thorough analysis.

4.2 Decoy Species

The decoy effect occurs whenever a third species interferes with the ability of a predator to detect or track its prey. It was described by Christensen et al. (1976) in a host–parasite system consisting of *Fasciola hepatica* (sheep liver fluke) miracidia, which infects the snail *Lymnaea trunculata*. The presence of non-host snails inhibits the ability of the parasite to find its host, depending in part on the non-host species (related/non-related). Similarly, Yousif et al. (1998) found that *Schistosoma mansoni* (schistosomiasis parasite) miracidia, which have the snail *Biomphalaria alexandrina* as host, were inhibited by the presence of several other snail species. More relevant to the study of predatory prokaryotes is the model for the decoy effect as described by Wilkinson (2001). This model is based on some attempts to use *B. bacteriovorus* and bacteriophages for pathogen control (Westergaard and Kramer 1977; Smith and Huggins 1983; Jackson and Whiting 1992; Fratamico and Whiting 1995; Sarkar et al. 1996). In particular, Drutz (1976) observed that *B. bacteriovorus* can waste time when encountering non-prey bacteria, in this case *Neisseria gonorrhoeae*. We essentially start at the model of Eqs. 23a–d and consider the addition of a non-prey species X_2, which is present at a constant level and has no direct effect on either X_0 or X_1. We make these assumptions to study the effect of the simple presence of a decoy species independently of any other competition effect. Rather than two states, the predator can now be in three states: free, bound to X_1, and bound to X_2. These complexes are denoted as $[X_1Y]$ and $[X_2Y]$. Again, assume the rate of collisions is r per unit of prey or non-prey species per unit of predator. Furthermore, the non-prey/predator complex dissociates at a rate of k_2. However, only the dissociation of the first complex yields new predators, again with a yield of $y_x + 1$. This leads to the following set of differential equations:

$$\frac{\mathrm{d}Y_{\mathrm{free}}}{\mathrm{d}t} = \left(y_x + 1\right) k_1[X_1Y] + k_2[X_2Y] - r\left(X_1 + X_2\right) Y_{\mathrm{free}} \tag{34a}$$

$$\frac{\mathrm{d}[X_1Y]}{\mathrm{d}t} = -k_1[X_1Y] + rX_1Y_{\mathrm{free}} \tag{34b}$$

$$\frac{\mathrm{d}[X_2Y]}{\mathrm{d}t} = -k_2[X_2Y] + rX_2Y_{\mathrm{free}}\,. \tag{34c}$$

At (quasi-)steady state we have

$$[X_1 Y] = \frac{r}{k_1} X_1 Y_{\text{free}} \quad \text{and} \quad [X_2 Y] = \frac{r}{k_2} X_2 Y_{\text{free}} .$$

Summing Eqs. 34a–c we find a growth rate of

$$\frac{\mathrm{d}Y}{\mathrm{d}t} = \frac{y_x k_1 X_1 Y}{k_1/r + X_1 + k_1 X_2/k_2} = \frac{\mu_y X_1 Y}{K_X + X_1 + K_{\text{inh}} X_2} , \tag{35}$$

with $K_X = k_1/r$ and $K_{\text{inh}} = k_1/k_2$. In this form we can recognize that the decoy effect is essentially a form of competitive inhibition (e.g. Vos et al. 2001; Wilkinson 2001). In effect the interference models of Beddington (1975) and DeAngelis et al. (1975) can be considered an *auto-decoy* effect. The above system could also be modelled using DDEs as in Eqs. 22a–d.

4.2.1 The Consequences for the Ecosystem

We can understand the consequences for the ecosystem by the usual analysis of the equilibria. The easiest way to do this is by absorbing the inhibition by the decoy into the saturation constant K_X. Substituting $K_X^* = K_X + K_{\text{inh}} X_2$ into Eqs. 21a–c we obtain equilibrium (in phase II or III) when

$$X_0 = \frac{1}{2}\left(S - K_1 - \frac{V_1 K_X^*}{\mu_y - D - d_y} \pm \sqrt{\left(S - K_1 - \frac{V_1 K_X^*}{\mu_y - D - d_y} \right)^2 + 4 K_1 S} \right) \tag{36a}$$

$$X_1 = \frac{\left(D + d_y\right) K_X^*}{\mu_y - D - d_y} \tag{36b}$$

$$Y = \frac{D}{D + d_y} \frac{\mu_y}{V_y} \left(\frac{\mu_1}{V_1} \left(S - X_0 \right) - X_1 \right) . \tag{36c}$$

Because the equilibrium density of X_1 is directly proportional to K_X^*, it should be a linear function of the density of decoys. Therefore, the decoy effect should be easy to quantify in an experimental setting, as suggested by Wilkinson (2001). To date, this has not been done. Figure 11 shows the stabilizing effect of decoys, with $K_X^* = 2K_X$. As can be seen, increasing K_X^* means that, for a given D, the predator can only be present in the ecosystem *at all* at a higher input substrate concentration than in the absence of decoys.

The decoy effect has been observed and modelled in the context of arthropod predator–prey systems (Vos et al. 2001). This model was slightly different in that multiple predator–prey couples were used, and some interference factor coupling these oscillators was postulated. For a more detailed review of the decoy effect in microbial and other ecosystems, see Wilkinson (2003).

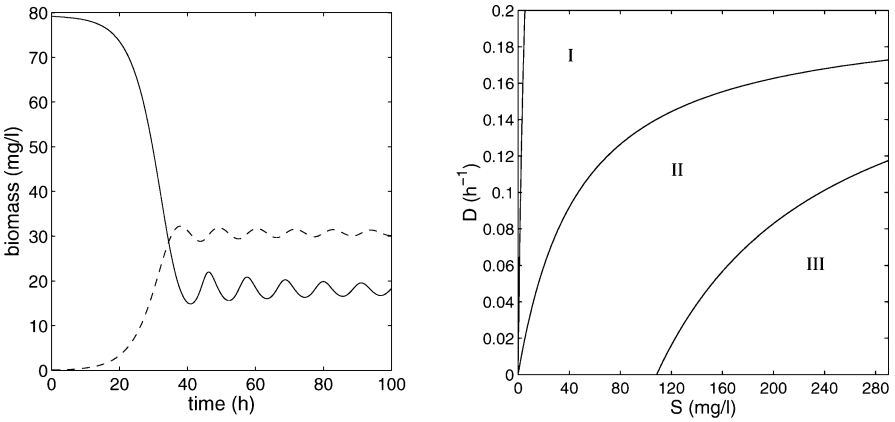

Fig. 11 The stabilizing effect of the presence of decoys, in the same system as shown in Fig. 3, shown for a decoy concentration such that $K_X^* = 2K_X$. **a** Transient behaviour shows damped oscillations between prey (*solid line*) and predator (*dashed line*); **b** phase boundaries show that the region of phase III (unstable oscillations) is greatly reduced with respect to Fig. 3b. See text for details

At this juncture it should be noted that the prey countermeasures suggested in Sect. 3.6, Eqs. 32a–e, do not include a decoy effect. Collisions between Y_{free} and X_1^* are not taken into account. It is expected that these would also lead to a decoy effect, further stabilizing the ecosystem and damping out oscillations.

4.3 Protector Species

The protector species effect is mainly known from nesting colonies of birds (Pius and Leberg 1998), in which a smaller, less aggressive species benefits from the presence of larger, more aggressive birds in the colony, if these latter (1) do not attack the smaller species and (2) are better at driving off potential predators than the smaller species. Mathematical models seem to be singularly lacking in this context, despite the fact that several of the above models could be adapted easily, by letting G depend on the density of the protector P, e.g.

$$G(X,Y) = \frac{gXY}{k_1 + X + k_2 P}\,, \tag{37}$$

which is yet again a form of competitive inhibition, similar to Eq. 15 or the decoy effect according to Eq. 34. Alternatively, the protector species effect may take a form similar to the Hassel and Varley (1969) or Arditi and Akçakaya

(1990) models, i.e.

$$G(X,Y) = \frac{gP^{-m}XY}{k_1 + P^{-m}X} . \tag{38}$$

I am not aware of any literature that describes this effect in microbes, and yet it is possible to imagine a similar effect happening in microbes. Suppose a third species produces a bacteriocin to which the predator is susceptible, but the prey is not. In this case the bacteriocin-producing species would act as protector species, albeit indirectly through the inhibitory or even bactericidal action of the bacteriocin. ODEs to model bacteriocins have been proposed by Frank (1994). Note that the phrase "protector species" is also used in a different context (Fisher and Freedman 1991), for which mathematical models do exist. In the case of Fisher and Freedman, no predator is modelled; rather, the protector species protects the environment of some other species, which in turn provides some sustenance to the protector.

5 Conclusions

Mathematical modelling of ecosystems, or even just single organisms, may seem a daunting task given the complexity of such systems compared to many systems in, e.g., physics. However, it is the very complexity of these biological systems which makes modelling an essential tool for their understanding. Highly complex systems consisting of many, much simpler, interacting units can be simulated with comparative ease on modern computers.

Fortunately, modelling predator–prey dynamics is a well-established field, and many effects have been studied. Furthermore, microbial predator–prey systems have many advantages compared to others, due to the short time scale at which dynamics such as oscillations occur, the small spatial extent and the degree of control, quite apart from the absence of ethical problems. As many authors have pointed out, chemostats offer an ideal system to observe the dynamics, and more importantly perform parameter estimation (Levin et al. 1977; Chao et al. 1977; Gerritse et al. 1992; Koch 1998; Kooi and Kooijmans 1994a). Many protist–bacterium, and bacteriophage–bacterium systems have been studied using such systems. Once parameters have been determined, they can be used to model the behaviour in real ecosystems with spatial extent (Jahnke et al. 1982; de Wit et al. 1995; Wilkinson 2002).

By contrast, mathematical modelling of predatory prokaryotes is in many ways still in its infancy. Very few articles provide models solely intended for these organisms (Marchand and Gabignon 1981; Dulos and Marchand 1984; Wilkinson 2001). On the other hand, the results from many other predator–prey models can be applied to these systems without major modifications.

Furthermore, many models already applied to bacteria, such as the bacteriocin model of Frank (1994) or Wilkinson (2002), can be adapted to model prokaryote predators.

One of the problems is the difficulty experienced in culturing many predatory prokaryotes in the laboratory (Martin 2002). Once these problems have been overcome, it should be possible to compare models, which are often easy enough to draw up, to the real dynamics observed in, e.g., a chemostat. Parameters estimated from such experiments could then be used to model the impact of these predators on, e.g., biofilm communities.

However, even without exact parameter estimates, strategic modelling can be used to gain some insight into the potential interactions. This is illustrated by the discussion on wolf-pack behaviour, modelled through Eqs. 24a–e. Even without real parameter estimates, we can determine that the two-species equilibrium in this system is so inherently unstable that the coexistence of two species is impossible. Therefore wolf-pack behaviour is unlikely to occur in obligate predators. In a way, we can consider mathematical modelling as a rigorous form of performing thought experiments in systems which are too complex to understand, or which exhibit counterintuitive behaviour. Many papers on microbial ecology describe the ecological effects of different parameters in the system qualitatively (Alexander 1981; Mallory et al. 1983; Shemesh and Jurkevitch 2004; Yair et al. 2003). I would not wish to claim these are at all wrong, especially when based on observation, or that we do not need a qualitative description. However, mathematical models can serve as a necessary "sanity check", if nothing else. They can also predict both the magnitude of the effects proposed and precisely under which conditions the effect should occur. Only with such quantitative predictions can we validate or invalidate our theories.

In this chapter a few new models have been put forward to model different types of predatory prokaryotes. Within the scope of this chapter it is impossible to analyse each of these models in detail, let alone provide a thorough validation. This must be left for future work. It might be objected that many of these models are somewhat speculative, and in some sense they are unashamedly so. However, the "speculations" made in this chapter do have a "mathematical backbone" which will help people to design experiments to prove the speculations right or wrong: if the latter, we will have to speculate anew.

I hope this chapter has served to illustrate some of the many factors which may complicate predator–prey dynamics. Many of these effects could occur in predatory prokaryotes, and drawing up suitable models is not very difficult. What is more difficult, and where many research opportunities lie, is in model validation and parameter estimation. Close collaboration between theoreticians and experimentalists in this area could lead to many new results and, of course, new questions.

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